REMARKS

Reconsideration is respectfully requested in light of the foregoing Amendment and remarks that follow.

Claims 1-4, 6, 7, 10, 16, 17 and 20-22 are before the Examiner. Claim 1 has been amended to further clarify the nature of the invention. Claim 14 has been cancelled. Claim 22, a Jepson claim, further highlights the improvement relative to the prior art of record.

Claims 7-9, 11 and 18-19 remain withdrawn from consideration by the Examiner as directed to a non-elected invention(s).

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention.

Withdrawal of the rejection is respectfully requested in light of the cancellation of claim 14.

Claims 1-4, 6, 10, 14 and 16-17 and 20-21 are rejected under 35 U.S.C. §103(a) as being unpatentable over Terwogt (Cancer Treatment Reviews, march 1997) or O'Brien (Annals of Oncology, 1992) in view of Ko (US 5,851,528) Applicants respectfully traverse.

Claim 1 has been amended to clearly set forth that the amount of complement activation inhibitor present in the therapeutic composition is sufficient to reduce the symptoms of the immediate hypersensitivity reaction caused by the presence of the specified amphiphilic carriers.

Terwogt et al. teaches that paclitaxel is active clinically against advanced ovarian and breast cancer. Terwogt et al. discloses a number of problems associated with paclitaxel, e.g. poor solubility in water and with a specific formulation, a mixture of ethanol and Cremophor EL. This formulation is indicated to cause some severe hypersensitivity reactions. (The specific nature of this reaction(s) is not detailed.) Terwogt et al. review some of the most promising formulation alternatives in their article- formulations devoid of Cremophor. There is no mention of the involvement of the complement system.

Ko et al. adds little to the relevant knowledge of Terwogt et al. article in terms of the involvement of the complement system in the immediate hypersensitivity reaction caused by the presence of specific amphiphilic carriers and the treatment of its symptoms. Ko et al. does disclose a chimeric molecules composed of a first and second polypeptides, both of which inhibit complement activation. The chimeric proteins are taught to reduce inflammation. Conditions

mentioned include those associated with ischemia-reperfusion, crash injury, burns, ARDS, autoimmune disorders, etc.. Table 1, previously referred to by the Examiner, lists potential clinical targets of the protein chimeras, i.e. targets to try. [1] None is an immediate complement reaction like that claimed. While the Table does mention "Drug Allergy", drug allergies come in a variety of types, e.g. delayed and causes, and also are not an immediate hypersensitivity reaction that results from the presence of polyethoxylated or a derivatized polyethoxylated oil-carrier, a non-drug.

O'Brien et al. reviews allergic reactions to cytotoxic drugs. Both Taxol and Cremophor are mentioned on page 609. It was reported by O'Brien et al. that in the phase I study, 2 of the first 5 patients who received Taxol as a 60-minute infusion developed anaphylactoid reactions during the first course. The other three patients developed less severe allergic symptoms during their second course. Cremophor was not proven to be the cause. The nature of the underlying mechanism is not stated by O'Brien et al. Infusion with antihistamines and pregnisole premedication is disclosed as causing the reaction to be less severe and less frequent.

As a first observation, the combined teachings are insufficient to lead one to treat the symptoms of an immediate hypersensitivity reaction due to the presence of polyethoxylated oil or a derivatized polyethoxylated oil carrier by the inclusion of complement activation inhibitor in the pharmaceutical composition containing the active ingredient. (The active ingredients are specified as taxol, paclitaxel, Doxil, althesin, cyclosporin, diazepham, didemnin E, echinomycin, propandid, steroids, teniposide, doxorubicin, daunorubicin, amphoterin B, hemoglobin, polynucleotide or a multivitamin.) None of the references unequivocally indicate polyethoxylated oil or a derivatized polyethoxylated oil carrier as the causative agent for an immediate hypersensitivity reaction. None of the references, alone or in combination, suggest the involvement of the complement system. Further, none of the references suggest the treatment of the claimed condition using a complement activation inhibitor.

Added to the noted deficiencies is the state of the art at the time the application was filed. As explained in the Background section of the present application, despite extensive use of

[1] The art of pathological conditions associated with complement activation in the field of complement prior to the instant disclosed invention are described in previously submitted Table A. Applicants consulted 44 reviews, research, or textbook articles in the field. Many of these reviews, both before and after 1998 (the Ko, et al patent issued on 22 Dec 98), gave comprehensive listing of pathological conditions associated with complement activation. Each of the pathological conditions mentioned by Ko, et al are included. The first mention of immediate non-IgE hypersensitivity reactions mediated by complement was published by Applicants in Feb, 1998.

Cremophor EL in pharmaceuticals, there was no consensus in the literature regarding whether any hypersensitivity was due to an active ingredient such as paclitaxel or to the vehicle, Cremophor EL, and how the hypersensitivity reaction is mediated (see pages 2 to 7 of the specification, particularly page 3, line 31 to page 4, line 4). This state of the art would impact a criteria of a prima facie case of obviousness "a reasonable expectation of success." In light of these uncertainties, enumerated in the specification as filed, it can hardly be said that there was the reasonable certainty of success as envisioned by statutory obviousness in contrast to "obvious to try." The Examiner is apparently employing the latter in assembling the art after the fact.

It is respectively submitted that a proper prima facie case has not been established for the reasons set forth above as to the invention as now claimed. Withdrawal of the rejection is respectfully requested.

In passing, the thrust of the arguments presented here are similar to those successfully presented to the European Examiner. The art applied by the European Examiner were arguably closer than those applied by the U.S. Examiner. (This art was previously submitted in an IDS.)

D4 (WO 97/268) is directed to concentrated injection and infusion solutions for intravascular use. Additives are used to mitigate delayed hypersensitivity reactions (page 1 lines 4 to 7). It is also stated in the desription of the invention (D4 page 4 lines 17 to 19) that D4 achieves "mitigation and avoidance of delayed hypersensitivity reactions" by the addition of substances having physical or pharmaceutical effects. On page 4 lines 6 to 8 of D4 a definition is given of "delayed reactions". These are defined as those side effects that occur only one or more hours after administration of the agent in question. Thus D4 clearly teaches the skilled person that any solution proposed in D4 is addressed to the problem of delayed hypersensitivity, by which is meant reactions occurring one or more hours after administration of the agent.

There is nothing in D3 (Michaud) or D5 (Terwogt) which suggests that Cremophor EL would be regarded by the skilled person as producing a hypersensitivity reaction of the type addressed by D4. On the contrary, D3 notes on page 1402, right hand column second paragraph "hypersensitivity reaction associated with Cremophor EL have historically been sporadic and rare occurrences."

D5 notes on page 89 lines 1 to 3 that: "studies have shown that the Cremophor EL vehicle induces histamine release and hypertension in dogs within 10 minutes after administration."

Accordingly, the skilled person would not consider the teachings of D3 or D5 to be relevant to the problem addressed by D4. The skilled person is therefore not taught by the prior

art that amphiphlic molecules produce a hypersensitivity which is mediated by complement activation. There is no suggestion in the prior art that a complement inhibitor could or should be used to inhibit, treat or reduce unwanted side effects caused by a pharmaceutical composition which includes a solvent or carrier amphiphilic molecules.

In view of the foregoing amendments and remarks, the application is believed to be in condition for allowance and a notice to that effect is respectfully requested.

Should the Examiner not agree that the Application to be in allowable condition or believe that a conference would be of value in expediting the prosecution of the Application, Applicants request that the Examiner telephone undersigned Counsel to discuss the case and afford Applicants an opportunity to submit any Supplemental Amendment that might advance prosecution and place the Application in allowable condition.

Respectfully submitted,

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